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Dockets Management Branch (HFA-305)
Food & Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

Docket No. 2004D-0465

Dear Sir/Madam:

The United States Pharmacopeia's Expert Committee on Gene Therapy, Cell Therapy and Tissue Engineering (GCT) are submitting comments on the Center for Biologics Evaluation and Research's (CBER's) draft "Guidance for FDA Review Staff and Sponsors: Content and Review of Chemistry, Manufacturing, and Control (CMC) Information for Human Gene Therapy Investigational New Drug Applications;" Docket No. 2004D-0465 (enclosed). Note that these comments are exclusively those of the Expert Committee and they have not been through the USP approval process.

You may contact me if you have any questions. On behalf of the GCT, thank you for the opportunity to provide input on this draft guidance. We hope these comments are helpful.

Sincerely,

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COMMENTS FROM:

USP's Expert Committee on Gene Therapy, Cell Therapy and Tissue Engineering (GCT)

On:

***Draft* Guidance for FDA Review Staff and Sponsors: Content and Review of Chemistry, Manufacturing, and Control (CMC) Information for Human Gene Therapy Investigational New Drug Applications (INDs)**

General comments:

1. This draft guidance is generally well written and contains useful information.

2. We understand that the gene therapy field is complex and rapidly evolving, and it is difficult to develop a totally comprehensive Guidance at this time. However, from the personal experiences of members of this Expert Committee in submitting INDs for gene therapy products, this Guidance document does not now reflect all current consensus CMC issues of major concern to CBER. We suggest that additional input from CBER reviewers to develop a more comprehensive list of CMC concerns and incorporate them into the Guidance.

3. The primary focus of this draft Guidance is ex-vivo, gene-modified cell therapy rather than on viral-vector or other, non-viral vector gene therapies. Ex-vivo gene-modified cell therapy is covered extensively in other CBER Guidances on somatic cell therapy (of which ex-vivo gene-modified cell therapy is a subset). We believe the Guidance would be more useful if it contained more information on viral-vector and non-viral vector gene therapies. In many areas of the Guidance, discussions of ex-vivo, gene-modified cell therapy could be replaced with the appropriate citation to previously established or drafted Guidances. Furthermore, there are numerous references throughout the document that imply that all types of gene therapy involve cells. As these are only a subset of types of gene-therapy products, these references should be changed to accommodate other types of gene therapies or, when appropriate, simply removed.

4. This Guidance is silent on the growing field of gene-therapy products using replicating vectors. We know that both DNA viruses (Adenovirus, Herpesvirus, AAV, Myxoma and Vaccinia) and RNA viruses (Reovirus, Newcastle Disease virus, Picornavirus, Sindbis Virus, Vesicular

Stomatitis virus, Measles, Retrovirus) are at least in the pre-clinical stages of development, with more than 20 clinical studies ongoing for some. We believe it would helpful if the issues surrounding the use of replicating viral vectors were addressed in this Guidance.

5. The Guidance should include a discussion of the use of available viral vector reference materials (i.e. Adeno and retrovirus).

6. The Guidance should indicate whether the various characterization tests should be performed under GLP conditions.

7. It may be more useful to sponsors and reviewers to break up the Guidance into shorter documents that address specific product categories (i.e. plasmids, retroviral vectors, adeno, AAV, gene-modified cells) and expand upon each area. There is precedence for this in Guidances covering other product areas.

8. The inclusion of both guidance for manufacturers and reviewers seems unusual and perhaps confusing.

Specific Comments:

1. Section III. A. 1. c (Sequence Analysis) – It would help to specify how this applies to RNA viruses, and at what stage of production a retrovirus vector sequence should be collected with respect to its application. For example, if used to generate stably transduced cell lines, should it be sequenced from the MCB? Furthermore, FDA should specify what sequences or types of sequences would be unacceptable for their presence in the product.

2. Section III. A. 2 (Cells) – This section should provide guidance on the methodology level of assay qualification and control. Also, a statement should be added regarding legacy cell lines in repositories (such as ATCC or tissue banking organizations) which may not have a high level of donor history or testing results documentation but can still validated per ICH Q5A (Viral Safety of Cell Lines) ref. 16.

3. Section III. A.2.b. 1) [Master Cell Bank (MCB)/Packaging Cell Line] – Does FDA consider an isozyme characterization an acceptable identity test? If yes, we suggest it be added to the list of acceptable test. If no, then the Guidance should specifically discourage its use. To our knowledge, isozyme characterization is one of the more widely used identification methods; however, we have some concerns over its utility. In addition, in the last bullet point regarding "Activity of cells," testing should only be performed if it is relevant to the therapeutic nature of the gene-therapy product. Furthermore, we believe that stability of the cell line upon repeat passage is an important characteristic and testing for it should be indicated in this section.

4. Section III. A, 2, b (Cell Bank System) – Banking of virus is discussed under this section title. For the sake of clarity, the banking of viruses should be transferred to section III.A. 1 (Vector). The stability of the viral vector after repeat passage should be demonstrated.

5. Section III. A. 3 (Reagents) – The USP has written General Chapter <1043> *Ancillary Materials for Cell, Gene, and Tissue-Engineered Products*. This General Information Chapter will become an official USP document with *USP*28, *First Supplement* (April 1, 2005) and contains a more extensive discussion of the characterization and qualification of ancillary materials (a.k.a. "reagents", the term used in this draft Guidance). We recommend that this Guidance reference this General Chapter as a source of additional information for both the sponsor and FDA reviewer. Also, as the items termed "reagents" (as defined here) are known by other names, this guidance should list the synonyms. Additional guidance should be given concerning the potential impact of using single source of reagents, vendor changes to reagent specifications and strategies of reducing their impact. Furthermore, additional guidance should be given on the use of reagents that are known or potential toxins or induce immunological reactions.

6. Section III, A, 3. d (Other Concerns) – It is our opinion that exposure of a cell line to penicillin during its derivation (i.e. explant from living tissue post biopsy) or a plasmid preparation (during selection in *E. coli*) used for transfection of stable cell lines for gene expression does not constitute use in manufacturing. However, we are of the understanding that such instances are frequently cited by some FDA reviewers as use of beta lactam antibiotics in manufacture and have resulted in significant protocol exclusion criteria. We suggest that the paragraph addressing the use of beta-lactams be revised to indicate that the use of beta-lactam is of concern only if it represents an actual risk of exposure to the gene therapy product. Furthermore, if a sponsor has determined that the use of beta-lactams in manufacturing is unavoidable, we believe the sponsor should be allowed to provide data or a theoretical argument regarding absence of risk to the patient.

7. Section III. B. 1 (Vector Production/Purification) and 2 (Preparation of ex Vivo Gene-Modified Autologous or Allogeneic Cells) – We recommend that the IND sponsor specify the harvest stage of the vector and of any ex-vivo, gene-modified cell.

8. Section IV. A. 1. b (Test Timing) – We believe that any reliance on Gram staining as a release test is unwise, as the technique is not easily validated and is highly dependent upon the experience and training of the personnel performing the test. Furthermore, we find the statement "If the final product is a genetically modified cellular therapy, and you cannot

complete 14 day sterility testing prior to administration, then we recommend that a sample of cells be taken 48-72 hours prior to final harvest or after the last re-feeding of the culture, and that you review the results of those sterility tests before you release the product," unclear. Our assumption is that the statement should read, in effect, "If the final product is a genetically modified cellular therapy, and you cannot complete 14-day sterility testing prior to administration, then we recommend that a sample of cells be taken 48-72 hours prior to final harvest or after the last re-feeding of the culture, that one of the prescribed or an alternate sterility test be performed on this sample, and that you review the results of the sterility tests before you release the product." If the foregoing reflects FDA's intent, we recommend that you change this sentence accordingly.

9. Section IV. A. 2 (Mycoplasma) and IV. A. 3 (Adventious Agent Testing) – These assays require substantial modifications when testing for the presence of mycoplasma and other adventious agents in replicating viral vectors (testing much diluted samples, using antibodies, etc), that can potentially affect the sensitivity of the assay. Additional guidance on how to deal with these issues would be helpful for both the IND sponsor and FDA reviewer.

10. Section IV. A. 3. c (Selected Species-Specific Testing for Adventitious Viruses) – We suggest that FDA provide guidance on what would be an acceptable approach to address adventious replication competent adenoviruses in a replicating adenoviral or other replicating gene therapy vectors. Does it become an issue of purity?

11. Section IV. A. 3. c. 2) (Testing for Retroviruses) – Please explain the significance of the 4-day period, as reflected in the following "In the case of ex vivo gene modified cells, if cells are cultured for $\geq$ 4 days, RCR testing would be appropriate. If ex vivo gene modified cells are cultured for < 4 days, archiving cells would be appropriate in place of active RCR testing."

12. Section IV. B (Identity) – We recommend that this section be expanded to cover vector identity tests and to include examples of what FDA would consider acceptable tests for the vector or any ex-vivo, gene-modified cells.

13. Section IV. C. 1 (Residual Contaminants) – In regards to testing for contaminating cell types or cell debris, we suggest that more information and guidance be given on what tests would be considered acceptable and how acceptable residual limits should be determined.

14. Section IV. C. 2 (Pyrogenicity/Endotoxin) – FDA should consider adding language to this section to address issues associated with the suitability